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SUBJECT:DEPO-PROVERA DENIED APPROVAL AS CONTRACEPTIVE IN US

THE FOLLOWING LETTER FROM FDA COMMISSIONER DONALD KENNEDY, PHD, WAS SENT TO THE HEALTH MINISTRIES OF 69 COUNTRIES WHERE THE CONTRACEPTIVE DRUG DEPO-PROVERA IS BEING USED OR HAS BEEN USED IN THE PAST. THE TEXT AS FOLLOWS IS FOR YOUR INFORMATION:

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"ON MARCH 8, 1978 THE UNITED STATES FOOD AND DRUG ADMINISTRATION (FDA) NOTIFIED THE UPJOHN COMPANY THAT APPROVAL HAD BEEN DENIED TO MARKET DEPO-PROVERA (MEDROXPROGESTERONE ACETATE) STERILE AQUEOUS SUSPENSION, 150 MILLIGRAMS, FOR USE AS AN INTRAMUSCULAR CONTRACEPTIVE FOR WOMEN IN THE UNITED STATES. THE DECISION WAS BASED ON THE GROUNDS THAT THE BENEFITS OF DEPO-PROVERA FOR CONTRACEPTION IN THE UNITED

STATES DO NOT JUSTIFY THE POTENTIAL RISKS TO THE USER.

FOR THE INFORMATION OF WORLD HEALTH ORGANIZATION MEMBERS, AND ALL OTHER INTERESTED PARTIES, THE CONSIDERATIONS ON WHICH FDA MADE THIS DECISION ARE AS FOLLOWS:

1. SAFETY QUESTIONS RAISED BY STUDIES IN BEAGLE DOGS SHOWING AN INCREASED INCIDENCE OF MAMMARY TUMORS ASSOCIATED

WITH THE DRUG HAVE NOT BEEN RESOLVED. BENIGN TUMORS IN DOGS OCCURRED AT THE HUMAN DOSE (ON A MG/KG BASIS), AND BENIGN AND MALIGNANT TUMORS OCCURRED AT 25 TIMES THE HUMAN DOSE OVER A PERIOD OF THREE YEARS. NO INTERMEDIATE DOSES WERE STUDIED. ALTHOUGH THE TUMORS AT THE HUMAN DOSE LEVEL WERE BENIGN THERE WERE TOO FEW ANIMALS TO ASCERTAIN THE PROPENSITY FOR MALIGNANCY AT DOSES LOWER THAN 25 TIMES THE HUMAN DOSE. OF THE 4 DOGS STUDIED AT THIS DOSE LEVEL ONLY 2 SURVIVED FOR AS LONG AS 5 YEARS.

THE U.S. MANUFACTURER OF DEPO-PROVERA CLAIMS THAT THERE DOES NOT APPEAR TO BE AN INCREASED INCIDENCE OF MAMMARY TUMORS IN WOMEN EXPOSED TO DEPO-PROVERA, BUT STUDIES HAVE BEEN INADEQUATE TO MAKE SUCH A CLAIM WITH ANY DEGREE OF CONFIDENCE.

2. THE AVAILABILITY IN THIS COUNTRY OF MANY SAFE AND UNCLASSIFIED

EFFECTIVE ALTERNATIVE METHODS OF CONTRACEPTION AND STERILIZATION LESSENS THE NEED FOR A LONG-TERM, POTENTIAL HIGH-RISK INJECTABLE CONTRACEPTIVE. NO CLEAR EVIDENCE HAS BEEN SUBMITTED TO SHOW THAT A SIGNIFICANT PATIENT POPULATION IN NEED OF THE DRUG EXISTS IN THE UNITED STATES. SINCE OCTOBER 1974, WHEN FDA STAYED THE ORDER PROVIDING FOR PATIENT LABELING FOR DEPO-PROVERA FOR CONTRACEPTION, TO THE PRESENT TIME, THERE HAS BEEN NO CLEAR DEMAND FROM THE MEDICAL COMMUNITY FOR DEPO-PROVERA FOR CONTRACEPTIVE USE.

3. IRREGULAR BLEEDING DISTURBANCES CAUSED BY THE DRUG OFTEN RESULT IN THE ADMINISTRATION OF ESTROGEN, IMPOSING AN ADDED RISK FACTOR AND DECREASING THE BENEFITS OF A PROGESTOGEN-ONLY CONTRACEPTIVE. ALTHOUGH THE USEFULNESS OF THIS APPROACH HAS BEEN DEBATED, ESTROGEN SUPPLEMENT FOR THE CONTROL OF BLEEDING HAS BEEN REPORTED IN NUMEROUS STUDIES, I.E., POWELL, L.C., AND SEYMOUR, R.J., AM. J. OBSTET. GYNECOL. 110:36, 1971 HARNECKER, J. ET AL., PROCEEDINGS OF THE SIXTH WORLD CONGRESS ON FERTILITY AND STERILITY, TEL AVIV, 1968, P. 27; AND EL-HABASHY, M.A., MISHELL, D.R. AND MOYER, D.L., OBSTET. GYNECOL. 35:51, 1970. THE USE OF ESTROGENS IN CASES WHERE THERE ARE

SEVERE BLEEDING DISORDERS ALSO HAS BEEN REPORTED BY DR. EDWIN B. MCDANIEL IN THE MCCORMICK HOSPITAL PROGRAM AT CHIANG MAI, THAILAND.

4. 4. EXPOSURE OF THE FETUS TO MEDROXYPROGESTERONE, IF THE DRUG FAILS AND PREGNANCY OCCURS, POSES A RISK OF CONGENITAL MALFORMATIONS. THIS RISK IS ENHANCED BY THE PROLONGED ACTION OF THE DRUG.

WE WISH TO EMPHASIZE THAT THE BENEFIT-RISK JUDGMENT MADE FOR THE UNITED STATES IS NOT NECESSARILY APPROPRIATE FOR OTHER COUNTRIES, AND THE FDA'S FAILURE TO APPROVE A DRUG DOES NOT NECESSARILY SIGNIFY THAT IT IS UNSAFE FOR CONTRACEPTIVE USE IN OTHER COUNTRIES. THE BALANCING OF RISKS
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AND BENEFITS IN DECIDING ON A PRODUCT'S APPROPRIATENESS SHOULD BE UNDERTAKEN BY EACH NATION IN LIGHT OF ITS OWN CIRCUMSTANCES AND NEEDS. WE RECOGNIZE THAT THE BENEFIT-RISK CONSIDERATIONS MAY NOT 3E THE SAME IN OTHER COUNTRIES OF THE WORLD AS THEY ARE IN THE UNITED STATES. NATIONS WITH A HIGHER BIRTH RATE, LOWER PHYSICIAN-TO-PATIENT RATIO, AND LESS READILY AVAILABLE OR ACCEPTABLE ALTERNATIVE CONTRACEPTIVE METHODS, WOULD OF COURSE HAVE DIFFERENT BENEFIT-RISK CONSIDERATIONS.

THE ADMINISTRATION RECENTLY SUBMITTED TO CONGRESS MAJOR NEW DRUG LEGISLATION THAT WOULD, AMONG OTHER THINGS, CHANGE THE CURRENT LAW GOVERNING THE EXPORT OF DRUGS FROM THE U.S. UNDER THE PROPOSED ACT, A DRUG UNAPPROVED FOR USE IN THIS COUNTRY COULD BE EXPORTED PROVIDED THAT THE DRUG MEETS THE SPECIFICATION OF THE FOREIGN PURCHASER, AND THAT THE GOVERNMENT OF THE COUNTRY OF DESTINATION HAS APPROVED THE IMPORTATION AND DISTRIBUTION OF THE DRUG. THIS IS ESSENTIALLY THE POLICY THE CONGRESS ADOPTED IN 1976 WHEN IT CONSIDERED THE EXPORT POLICY FOR MEDICAL DEVICES IN THE MEDICAL DEVICE AMENDMENTS.

THE PROPOSED DRUG LEGISLATION ALSO PROVIDES FOR ASSISTANCE TO FOREIGN GOVERNMENTS LACKING THE TECHNICAL RESOURCES TO EVALUATE THE SAFETY AND EFFICACY OF A DRUG OFFERED TO IT. THE BILL AUTHORIZES THE EXCHANGE OF DRUG INFORMATION IN OUR POSSESSION WITH FOREIGN HEALTH OFFICIALS AND INTERNATIONAL ORGANIZATIONS SUCH AS THE WORLD HEALTH ORGANIZATION. THE CURRENT LAW'S EXPORT PROHIBITIONS DENY POTENTIAL BENEFITS TO BOTH THE HEALTH AND SCIENTIFIC CAPABILITIES OF FOREIGN NATIONS.

EVEN WITHOUT THE PROPOSED NEW AUTHORITIES, WE ARE IN A
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POSITION TO PROVIDE ASSISTANCE TO FOREIGN GOVERNMENTS IN HELPING THEM TO MAKE DECISIONS ABOUT DRUGS. IN THE CASE OF DEPO-PROVERA, FOR EXAMPLE, WE RECENTLY MET WITH A REP-RESENTATIVE OF THE WORLD HEALTH ORGANIZATION AND OFFERED TO PROVIDE SUMMARIES OF OUR EVALUATIONS OF THE SAFETY AND EFFICACY DATA OF THIS DRUG, TRANSCRIPTS OF ADVISORY COMMITTEE MEETINGS DURING WHICH BENEFIT/RISK CONSIDERATIONS WERE WEIGHED, AND OTHER DATA THAT MIGHT ASSIST FOREIGN COUNTIRES IN DECIDING WHETHER TO IMPORT IT. TO THE EXTENT

WEARE ABLE, WE WILL CONTINUE TO COOPERATE WITH THE WORLD HEALTH ORGANIZATION AND OTHER APPROPRIATE ORGANIZATIONS BY PROVIDING DATA ON THIS OR ANY OTHER DRUG OR DEVICE BEING CONSIDERED FOR USE IN OTHER NATIONS." VANCE

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